REMARKS/ARGUMENTS

I. Status of the claims

With entry of this Amendment, claims 2-3, 14, and 27-66 are canceled and claims 1, 7-10, and 25-26 are amended. Claim 6 was canceled previously. Claims 1, 4-5, 7-13, and 15-26 are pending with entry of the Amendment.

II. Support for the amendments

Support for the amendments can be found in the specification, Figures and original claims. For example, support for claim 1 can be found, for example, in original claims 7-12 and paragraphs 132-134 of the specification. Support for the amendments to claims 7-10 merely insert sequence identifiers and do not change the claim scope. No new matter is added.

III. Objection to the claims

The Examiner objected to claims 7-10 as failing to comply with the sequence rules. As amended, the claims include sequence identifiers. Withdrawal of the objections is respectfully requested.

IV. Rejection under 35 USC § 112, first paragraph: enablement

The Examiner rejected claims 1-5, 7-15, 18-21, and 25-26 as allegedly not enabled. Specifically, the Examiner argued that the specification enabled *L. jensensii* comprising an expression cassette coding for 2D-CD4 linked to a cell wall anchoring sequence selected from C14 and C370, but did not enable broader subject matter. *See*, Office Action, page 4. To the extent the rejections apply to the amended claims, Applicants respectfully traverse the rejection.

The amended claims are directed to *L. jensensii* comprising an expression cassette coding for a biologically-active polypeptide linked to a cell wall anchoring sequence selected from C14 and C370, i.e., SEQ ID NOs: 7 and 8, respectively. Thus, in many aspects, the claims correspond to the subject matter the Examiner acknowledged as enabled. Nevertheless, there are

some differences between the amended claims and the subject matter acknowledged by the Examiner and so the following analysis is provided.

Biologically active protein

The Examiner argued in the Office Action that the specification was not enabled for any biologically-active polypeptide, but instead was limited to the 2D-CD4 polypeptide exemplified in the Examples of the specification. The basis of the Examiner's arguments appears to be that predicting the three-dimensional structure of a protein can be difficult. *See*, Office Action, pages 7-9. The Examiner's emphasis on the three-dimensional structure of biologically active polypeptide appears to be misplaced. Further, the citation of papers in the Office Action related to EGF and hormone structure is not relevant to the presently claimed invention.

The present invention centers on the discovery of sequences useful for secretion and cell-wall anchoring of proteins in *Lactobacillus*. It is common molecular biology practice to use signal sequences and anchoring sequences to direct proteins to cell membranes or cell walls depending on the signal or anchoring sequences used. Such fusions do not generally affect activity of the protein to which the signal or anchoring sequences are fused. *See*, e.g., Samuelson *et al.*, *J. Biotechnol.* 96 (2002): 129-154, abstract ("Display of heterologous proteins on the surface of microorganisms, enabled by means of recombinant DNA technology, has become increasingly used strategy...") and Strauss and Gotz, *Molec. Microbiol.* (1996) 21(3):491-500, abstract ("These results demonstrate that it is possible to immobilize normally soluble enzymes on the cell wall of *S. carnosus* - without radically altering their catalytic activity - by fusing them to a cell-wall-immobilization unit ..."), both of which were cited by the Examiner. The use of signal sequences is generally not dependent on the structure of protein to which it is fused. Thus, Applicants submit that there is no scientific reason to question whether the signal sequences identified in the present application work for biologically-active proteins in general, rather than only the exemplified 2D-CD4. Indeed, it should be noted that the examples of the specification demonstrate appropriate protein localization with C-myc as well as 2D-CD4 (*see, e.g.*, paragraph 123 of the present specification), indicating that the signal sequence functions independent of the protein fused to the signal sequence. Accordingly, Applicants submit that the specification

enabled those of ordinary skill in the art to make and use the claimed invention across all biologically active proteins.

LPQTG variants

The Examiner indicated that the specification was enabling for the constructs as "more specifically set forth in the examples." *See*, Office Action, page 4. It is not clear whether the Examiner has acknowledged the enablement of the variants of the LPQTG motif as set forth in original claims 7-10 and newly amended claim 1. Therefore, in an abundance of caution, Applicants will explain enablement of this aspect here.

As explained in the specification and examples, the native sequences derived from *L. jensenii* (C14 and C370) include the signaling motif LPQTG. However, the inventors describe modification of that motif to, among others, the variants currently recited in claim 1. For example, paragraphs 132-134 as well as Figure 9 demonstrates that the variants recited in the claims are functional variants of the LPQTG motif in the context of the C14 and C370 sequences. Figure 9 in particular summarizes the data and shows that the recited variants were each effective in directing fusion proteins to the cell surface. Thus, there should be no question regarding the enablement of these variants.

Conclusion

The amended claims are enabled across their full scope. As the detailed analysis in the Example sections demonstrates, the recited cell wall sequences are effective at directing protein to the cell surface regardless of the fused proteins sequence. Accordingly, Applicants respectfully request withdrawal of the rejection.

V. Rejection under 35 USC § 112, first paragraph: written description

The Examiner rejected claims 1-5, 7-10, 13-15, 18-21, and 25-26 as allegedly not complying with the written description requirement. The Examiner's concerns regarding written description appeared to be that the claims encompassed "a genus of polypeptide and cell wall associated sequences[s]." *See*. Office Action, page 12. The Examiner indicated that the

specification did not provide "any specific guidance" with regard to "the size of [the] cell wall targeting region or cell wall associated sequence." *See, id.* The Examiner further argued that minor structural changes in proteins can result in large changes in activity. For this proposition, the Examiner relied on the Ngo *et al.* reference, which published 10 years before the filing date of the present application and is directed to somewhat theoretical issues related to computer modeling of protein structure. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The Examiner correctly states (citing *Vas-cath*) that the written description requirement requires that the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." However, in *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), the Federal Circuit confirmed that every species in a genus need not be described. The Federal Circuit required that the specification provide "structural features commonly possessed by members of the genus that distinguish them from others" (Emphasis added). *Id.* The Examiner is reminded that the standard is of teaching "the structural features of the chemical genus that distinguish it from other chemical structures" not writing out every possible sequence and showing that each one separately works!

The amended claims are directed to *L. jensensii* comprising an expression cassette coding for a biologically-active polypeptide linked to a cell wall anchoring sequence selected from C14 and C370, i.e., SEQ ID NOs: 7 and 8, respectively. By reciting SEQ ID NOs: 7 or 8, the claims include a specific cell wall associated sequence that has been shown to function (i.e. to localize a heterologous fused protein sequence). As discussed in detail above with regard to enablement, the use of signal sequences is generally not dependent on the structure of protein to which it is fused and this is confirmed in a review of the art cited by the Examiner. Thus, the detailed examples provided in the present specification demonstrate to those of skill in the art that the full scope of the claimed invention (i.e., the use of SEQ ID NOs: 7 or 8, or variants thereof shown in the examples to localize heterologous proteins to the cell surface in *L. jensenii*) was in the possession of the inventors when the application was filed.

Accordingly, the examples in the patent application show that the inventors were in possession of the claimed invention. Therefore, withdrawal of the rejection is respectfully requested.

VI. Rejection under 35 USC § 112, second paragraph

a. "Cell wall associated sequence"

The Examiner did not explain specifically what words were unclear in rejecting the clarity of claim 1, but argued that it was not clear "how the sequence is associated with cell in the cell wall targeting region." *See*, Office Action, page 15. Applicants believe that rejection relates to the use of "cell wall associated sequence" in the original claims. As that phrase does not occur in the amended claims, Applicants respectfully request withdrawal of the rejection.

b. "Charged sequence"

The Examiner rejected claim 4 as allegedly unclear for reciting "further comprises a charged sequence at the carboxyl terminus of region." The Examiner argued that the cell wall region as recited in claim 1 comprises a hydrophobic sequence and argued that the hydrophobic region was a charged region and so did not further limit the claim.

As an initial matter, it should be noted that hydrophobic sequences in general *lack* charged sequences(amino acids are generally hydrophobic *or* charged, but not *both*) and thus to the extent the rejection relies on hydrophobic sequences comprising charged sequences, the rejection is inappropriate. Nevertheless, to expedite prosecution, claim 4 is amended to recite specific charged sequences, as described for example in paragraphs 76-77 of the specification. Applicants have also corrected antecedent basis by including "the cell wall targeting" before "region".

VII. Prior art rejections

The Examiner rejected a number of the claims as allegedly anticipated or rendered obvious by the prior art. While Applicants do not agree with the Examiner's analysis, to expedite prosecution, claim 1 has been amended to include the sequences (SEQ ID NOs: 7 and 8) recited

in claims 11 and 12. As claims 11 and 12 were not rejected as anticipated or obvious, Applicants submit that amended claim 1 is free of the prior art. Accordingly, withdrawal of the rejections is respectfully requested.

VIII. Provisional obviousness-type double patenting rejection

The Examiner rejected claims 1-5, 7-15, 18-21 and 25-26 as allegedly unpatentable under obviousness-type double patenting in view of U.S. Patent Application 11/620,588. The rejection is a provisional rejection.

As the rejection is a provisional rejection, it is Applicant's understanding that he claims can issue if this is the only remaining rejection. Applicants request that the rejection be held in abeyance until that time.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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